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(54) Title: ENTERIC COATED PHARMACEUTICAL FORMULATION

(57) Abstract: A method of making an oral pharmaceutical dosage form of an aqueous soluble drug including the steps of: forming a solution or suspension of the drug, a soluble polymer and a binding or gelling agent; contacting the solution or suspension with an acid precipitating medium allowing the polymer to precipitate to form particles containing the dissolved drug; drying the particles; wherein the gelling or binding agent influences or prevents migration of the drug towards the surface of the particles during drying.

ENTERIC COATED PHARMACEUTICAL FORMULATION

This invention relates to enteric coated pharmaceutical formulations and methods of production.

Some drugs when given orally should not be released immediately into the stomach but should be formulated so that they are only available for absorption in the upper or lower intestine or colon. The reasons for a delay until they are passed out of the stomach vary, but include: instability in an acid medium, for example omeprazole; possible erosion and damage to the stomach wall by non-steroidal anti-inflammatory drugs for example diclofenac and gastric upset, for example some erythromycin salts.

The normal means of preventing such problems is by coating a tablet containing the drug with an enteric layer. An enteric layer is a coating of a substance which is insoluble in the acid medium of the stomach but which is soluble at the higher pH encountered in the intestine. Such materials are used as film coatings on tablets. Suitable film coating materials include methyl methacrylate polymers (as sold under the trade mark Eudragit), cellulose acetate phthalate, polyvinyl acetate phthalate and hydroxypropyl methyl phthalate. However there is a problem with such tablets, particularly larger tablets because they may be retained in the stomach for a considerable time, for example 4 to 8 hours, before release into the intestine. Such retention is unsuitable for drugs where prompt action is desired or where the absorption and blood levels should be maintained at a constant value.

It has been reported that some of these problems can be overcome with multiparticulate systems, wherein the dosage

form breaks down in the stomach to form significantly smaller particles which pass through the stomach more quickly and reproducibly.

Usually such dosage forms are capsules containing multiple particles, pellets or tablets. Such particles, pellets or tablets may consist of a core containing the drug with an overcoating of an enteric film. The core may be a conventional tablet, an extruded bead containing the drug or a non-pareil overcoated with a layer of drug. Capsules are widely used but have the drawback that the dosage cannot be varied easily as with a conventional tablet with a score-line which enables the tablet to be reasonably accurately divided into two or more parts containing known quantities of drug. Attempts have been made to produce tablets containing multiple particles but in many cases these have been unsatisfactory because the coated bead either does not deform enough to bind within a tablet or if it does deform, it causes failure of the enteric film due to cracking etc.

An alternative approach has been disclosed by H C Zaniboni, J T Fell and J H Collett (International Journal of Pharmaceutics 125 (1995) 151-155). The authors disclosed manufacture of enteric particles by precipitation of the enteric polymer hydroxypropyl methyl cellulose phthalate in aqueous citric acid. However problems were found with water soluble compounds due to migration during the drying process. Deposition of significant quantities of drug on the outside of the particles facilitates rapid dissolution in acid conditions leading to very high dosage or burst effect.

According to a first aspect of the present invention a method of making an oral pharmaceutical dosage form of a drug includes the steps of:

forming a solution or suspension containing the drug, a soluble polymer and a binding or gelling agent,

contacting the solution or suspension with an acid precipitating medium, allowing the polymer to precipitate to form particles containing the dissolved or suspended drug,

drying the particles,

wherein the gelling or binding agent retards or prevents migration of the drug towards the surface of the particles during drying.

The particles may be incorporated into a tablet or filled into a gelatin capsule.

The solution or suspension may be formed into drops and the drops are contacted with acid medium. Alternatively the solution may be added directly into the acid medium with stirring or agitation to give the particles. The particles may comprise a fine powder suitable for formulation.

According to a second aspect of the present invention an oral pharmaceutical dosage form comprises a drug, a soluble polymer, a gelling or binding agent and one or more inert excipients, the gelling or binding agent being adapted to retard or prevent migration of the drug towards a surface of the dosage form. The dosage form preferably comprises a tablet or capsule containing particles of the formulation. Alternatively the dosage form may comprise an undried or partially dried particle for use in manufacture of such a tablet or capsule.

The particles may be formed by sonicating or other pressure wave methods to break up the stream of drug/polymer solution as it enters the acid medium.

A preferred soluble polymer is hydroxypropyl methyl cellulose phthalate (HPMCP). This polymer is suitable for enteric coating applications because it is insoluble in gastric fluid but dissolves rapidly at the higher pH values

found in the small intestine. A preferred grade of HPMCP is HP-50 manufactured by Shin-Etsu Co Ltd. This polymer may be precipitated in accordance with the invention by contacting the drops or solution with aqueous acid, for example 5 to 20% preferably 10 to 15% citric acid.

Percentages or amounts referred to in this specification are by weight unless indicated otherwise.

Other suitable polymers which may be used include methyl methacrylate polymers (as sold under the trade mark Eudragit), cellulose acetate phthalate, polyvinyl acetate phthalate and hydroxypropyl methyl phthalate.

A variety of binding or gelling agents may be employed, including polymers, cellulosic materials, sugars, coacervating and complexing agents. Polyvinyl pyrrolidone (PVP) preferably with a molecular weight in the region of 30,000 is preferred. PVP has been found to be beneficial in solubilising drugs such as diclofenac, particularly in combination with HPMC. Methacrylate acid esters and gelatin also may be used. Cellulosic polymers including hydroxypropyl methyl cellulose, methyl cellulose and cellulose suspensions. Other compounds include cyclodextrins, polydextroses and modified starches.

In preferred formulations the amount of the gelling agent may lie in the range 1 to 50% w/w of the weight of formulation. An amount of 1 to 10%, preferably 6 to 8% by weight may be particularly suitable.

In preferred embodiments of the first aspect of this invention the solution or suspension containing the drug, soluble polymer and binding or gelling agent comprises an aqueous solution or suspension including the following:

5 - 20%, preferably about 10% of a drug selected from diclofenac and proton pump inhibitors for example omeprazole, lansoprazole, pantoprazole and rabeprazole;

5 - 20% of polyvinylpyrrolidone;

10 - 20%, preferably 12 - 15% of hydroxypropylmethyl cellulose phthalate.

These compositions result in particles which are not sticky after drying. Use of 5 - 10% polyvinylpyrrolidone, especially 7 - 8% together with 12 - 15%, preferably 14% HCMCP is preferred for formation of evenly shaped oval or spherical non-sticky particles.

Materials which may be cross-linked by photolysis may also be employed, for example 2-hydroxyethyl methacrylate. In this case the method of production of the dosage form includes the step of exposing the particles to photolytic radiation prior to drying in order to cause the gelling and binding agent to cross-link.

Alternative formulations incorporate one or more water absorbing agents, for example a partially hydrated hydrogel adapted to absorb the drug containing aqueous solution within the core of the bead during drying. A partially hydrated hydrogel may be added to the concentrated drug/polymer solution immediately prior to precipitation of the particles.

The drying technique is preferably selected to minimise migration of the drug during evaporation.

Drugs suitable for formulation in accordance with this invention include diclofenac and proton pump inhibitors including omeprazole; lansoprazole, pantoprazole and rabeprazole; sodium valproate; steroids; antibiotics etc. Aqueous soluble drugs may be formulation from solution. Insoluble or poorly soluble drugs may be formulated from suspensions.

An amount of 0.2 - 10% diclofenac, preferably 1 - 10% w/v is preferred in the initial solution or suspension. The

amount of drug chosen may be selected to give an appropriate dosage in the final product. The

The method in accordance with this invention may be selected so that the rate of formation of the particles is accelerated to reduce diffusion of the drug during the formation of the particles. Precipitation of the polymer may be enhanced using an acid, for example hydrochloric acid which is stronger than the previously employed citric acid. This results in more rapid particle formation, reducing the liability to drug diffusion during the precipitation step.

Once the particles are dry they may be filled into capsules or mixed with inert excipients and compressed into tablets. The inert excipients may also include another active substance or substances if a product is required with two or more drugs where only one needs enteric coating. For example diclofenac with misoprostol.

The inert excipients will include fillers, binders, lubricants, colours and will preferably include microcrystalline cellulose which has good carrying capacity for the particles.

Tablets in accordance with this invention may be provided with one or more break lines to facilitate division into smaller doses. They may also be over coated with a standard film or sugar coating in case of taste problems, light instability or discolouration of the tablets.

If a varied release profile in the intestine is required, a mixture of particles from different batches with different amounts of polymer may be used. Methacrylate polymers are preferred for this aspect. In this aspect, uncoated drug fine powder may be added to the tablet mixture to give some immediate release of drug.

The invention is described by means of example, but not in any limitative sense.

EXAMPLE 1 - Preparation of HPMCP Macroparticles

A polymer solution was prepared by dissolving HPMCP (2-10 %w/v)and polyvinyl pyrrolidone (PVP) in an alkaline solution of sodium bicarbonate (2 %w/v). Particles were formed by adding ~10 ml of the HPMCP dropwise, into ~100 ml of citric acid solution (5-25 %w/v) at a temperature of *ca* 0-5°C with constant stirring.

After the HPMCP was added the emulsion was left to continue stirring for a further 2 hr, after which the particles were filtered off and washed 3 times with distilled water. The particles were dried in a freeze-drier for at least 12 hr.

In the first instance, no drug was used in the preparation in order to compare particles made on a low speed laboratory stirrer with a Silversun high speed stirrer. The most effective recipes were used in the preparation for drug loaded particles. The drug used for these preparations was diclofenac.

EXAMPLE 1A

LOW SPEED STIRRER:

Tables 1-3 show the formulations used in the preparation of particles on a low speed stirrer.

Table 1. Recipes for low speed stirrer.

HPMCP/% w/v	2	5	10
Citric Acid/% w/v	5	5	5
Stirring speed/rpm (approx)	300	300	300

Particles made from 2% w/v HPMCP did not form as the solution was viscous enough for the particles to maintain their form in the emulsion medium. 5% w/v HPMCP particles were elongated in the shape but the 10% w/v particles were rounded.

Table 2.

HPMCP	10	10	10
Citric Acid/% w/v	5	15	25
pH of citric acid at *ca* 0.5°C	2.4	2.0	1.8
Stirring speed /rpm (approx)	300	300	300

Particles were all rounded in shape but in the case of the highest concentration of citric acid (25% w/v) the dried particles appeared glassy in colour and sticky rather than opaque and dry as for the others. They also appeared slightly shrunken in size by comparison. 15% w/v citric was considered to give the best particles.

Table 3.

HPMCP	10	10	10
Citric Acid/% w/v	5	5	5
Stirring speed/rpm (approx)	300	300	300

The particles produced on the lower 2 speed settings were relatively evenly shaped (especially the 15% w/v citric prepared on the lowest speed; 300 rpm) as the speed is increased to >650 rpm the shapes are irregular and elongated.

EXAMPLE 1B - Silversun Stirrer

Particles were prepared in the same way on the Silversun mixer as for the low speed mixer described above except a larger vessel for the preparation was used and a larger volume of citric acid due to the requirements for high speed mixing.

Formulations for the preparation were as shown in Table 4.

Table 4.

HPMCP/% w/v	Citric Acid/% w/v	Speed setting*	Comment
5	5	1	Particles not formed
10	5	1	some, uneven particles
		2	some oval particles
		3	uneven, oval particles and unformed polymer
10	15	1	white, even coloured and spherical particles
		2	white, even coloured, but some oval particles
15	5	1	some glassy-looking particles
		2	some glassy-looking particles
15	15	1	some glassy-looking, sticky particles
		2	sticky, round particles

* 3<2<1

5% HPMCP formulation did not form particles due to the low viscosity of the polymer solution and the droplets not holding their shape under the high shear of the mixing process. Of the particles prepared on the highest speed setting (3), although some were well formed and spherical in shape, there were also some misshapen, oval shaped particles and a proportion of the polymer did not form any particles. The third speed setting was not preferred due to the large

volume of citric acid and the size of the container required to produce a reasonable emulsion medium.

The particles obtained indicated that an increase in the concentration of the polymer solution improved the shape of the particles but could result in some glassy particles and slight stickiness. Increasing the citric acid content did not appear to have a significant affect on the particles except when the HPMCP concentration is also high as this resulted in sticky particles. Increasing the speed appeared to have a negligible effect on the size and shape of the particles.

EXAMPLE 2 - Diclofenac Sodium Particles

Preparation of Particles

Particles using PVP as a gelling agent may be prepared in the same way as described previously. Diclofenac sodium may be introduced into the bead formulation in the following ways:

1) Suspended or dissolved in the HPMCP solution
2) Dissolved in $NaHCO_3$ solution prior to preparation the HPMCP solution, (max solubility of diclofenac in $NaHCO_3$ = 2.6 mg/ml [0.26% w/v])
3) Dissolved in ethanol and added to $NaHCO_3$ solution (approx max solubility of diclofenac in ethanol = 0.1 g/ml [10% w/v]).

Concentrations of $NaHCO_3$ and citric acid solutions used were 2% and 5% w/v respectively.

Bead Formulations

Sample	HPMCP/% w/v	diclofenac*/% wv	ethanol/ cm^2	stirring speed	result
Drug suspension particles:					
A	10	2	-	1st	F
B	10	2	-	2nd	N/F
Dissolved in $NaHCO_3$ solution:					
C	10	0.2	-	1st	1/2F
Dissolved in ethanol:					
D	10	2	20	1st	N/F
E	15	2	20	1st	N/F
F-1	15	1	10	1st	F
F-2	15	1	10	1st	1/2F

* In total volume of polymer solution

F = particles were formed

1/2F = not all polymer formed particles, some polymer debris remained amongst particles collected

N/F = particles were not formed

The characteristics of particles produced using different concentrations of diclofenac were investigated. Formulations using 10% HPMCP, 7.5% PVP and 1 and 2% diclofenac sodium were dissolved in 2% $NaHCO_3$ and with 3, 5 and 10% diclofenac were suspended in 2% $NaHCO_3$. Particles were precipitated using 15% citric acid. All formulations produced uniform beads. Formulations with 3 and 5% diclofenac produced uniform spherical beads and with 10% hard uniform spherical beads were produced.

EXAMPLE 3 - Encapsulation of Diclofenac in HPMCP particles:

0.2 g of particles were redissolved in 10 cm^2 of the 2% w/v $NaHCO_3$ solution (0.02% w/v). The samples that did not dissolve to produce a clear solution were filtered. The solution was diluted 1 in 100 and the absorption 275.7 was measured and compared to a previously constructed calibration of diclofenac sodium in $NaHCO_3$ solution. Equivalent blank particles prepared from 10 and 15% w/v HPMCP were also analysed in this way and the results subtracted from values for the drug loaded particles. The results are shown in the following table.

Sample	Theoretical % drug entrapment	Actual % entrapment	Entrapment efficiency
A†	16.7	6.6	39.7
B*†	16.7	7.3	43.8
C	2.0	1.1	57.6
D*†	16.7	9.2	55.2
E*†	11.8	6.4	54.7
F-1	6.2	5.0	79.8
F-2	6.2	4.5	72.8

* No particles were formed

† Sample did not dissolve and had to be filtered.

Bead formation and highest entrapment efficiency was achieved when first dissolving the diclofenac sodium in ethanol and then mixing with the $NaHCO_3$ solution in the ratio 10/90 ethanol/$NaHCO_3$ solution, prior to dissolving the HPMCP. As the volume of ethanol increases the viscosity of the polymer solution decreases and particles are not formed.

CLAIMS

1. A method of making an oral pharmaceutical dosage form of a drug including the steps of:

forming a solution or suspension containing the drug, a soluble polymer and a binding or gelling agent;

contacting the solution or suspension with an acid precipitating medium allowing the polymer to precipitate to form particles containing the dissolved or suspended drug;

drying the particles;

wherein the gelling or binding agent retards or prevents migration of the drug towards the surface of the particles during drying.

2. A method as claimed in claim 1 wherein the particles are incorporated into a tablet or filled into a gelatin capsule.

3. A method as claimed in claim 1 or 2, wherein the solution or suspension is formed into the drops and the drops are contacted with the acid precipitating medium.

4. A method as claimed in any preceding claim, wherein the soluble polymer is hydroxypropyl methylcellulose phthalate.

5. A method as claimed in any preceding claim, wherein the acid precipitating medium is citric acid.

6. A method as claimed in claim 5 wherein the acid precipitating medium is 5 to 20% citric acid.

7. A method as claimed in claim 6 wherein the acid precipitating medium is 10 to 15% citric acid.

8. A method as claimed in any of claims 2 or 3 wherein the soluble polymer is selected from: methylmethacrylate polymers, cellulose acetate phthalate, polyvinyl acetate phthalate and hydroxypropyl methyl phthalate.

9. A method as claimed in any preceding claim, wherein the binding or gelling agent is selected from: polyvinylpyrrolidone, methacrylate acid esters, gelatin, cellulosic polymers, cyclodextrins, polydextroses and modified starches.

10. A method as claimed in claim 9 wherein the amount of binding or gelling agent is 20 to 200% of the weight of the soluble drug.

11. A method as claimed in claim 9, wherein the binding or gelling agent is polyvinylpyrrolidone.

12. A method as claimed in claim 11, wherein the solution containing the drug, soluble polymer and binding or gelling agent comprises an aqueous solution or suspension including the following:

1 - 20% of a drug selected from diclofenac, omeprazole, lansoprazole, pantoprazole and rabeprazole;

1 - 12% polyvinylpyrrolidone;

1 - 20%, preferably 12 - 15% hydroxypropylmethyl cellulose phthalate.

13. A method as claimed in claim 12, wherein the drug is diclofenac in an amount of 3 - 10%.

14. A method as claimed in any preceding claim, wherein the formulation includes a partially hydrated hydrogel.

15. An oral pharmaceutical dosage form comprising particles formed from a soluble or suspended drug, a soluble polymer, a gelling or binding agent and one or more inert excipients, the gelling or binding agent being adapted to influence or prevent migration of the drug towards a surface of the dosage form.

16. A tablet or capsule containing or incorporating a dosage form as claimed in claim 15.